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MEDICAL DIVISION REPORT NO. 105

THE ORAL TOXICITY OF HEXAVALENT CHROMIUM

by

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Publication Control No. 5030-105

Medical Division Report No. 105. The Oral Toxicity of Hexavalent Chromium.

ABSTRACT

OBJECT.

The object of this investigation was to determine the effect on albino rats of the oral ingestion of water containing hexavalent chromium.

RESULTS.

1. Water consumption in all three test groups fell off, the decrease being progressively greater with increasing concentration of chromium, due to the reduced palatibility of the water. After several days on the chromium contaminated water, all three groups apparently learned to tolerate the water. Their water consumption then continued at a rate somewhat lower than that of the control rats.

2. The rate of growth of Groups II, III, and IV, after being checked for two or three days following the first feeding of chromium, continued, with deviations probably due to pneumonia, to parallel the growth curve of the control group.

3. The only pathology found in the rats was the occasional presence of pneumonia. This finding appeared in both the experimental and control animals. Therefore, it can not be said that potassium dichromate was the causative factor in the production of pneumonia.

CONCLUSIONS.

1. The test animals drank concentrations of hexavalent chromium as high as 200 mg./l. as potassium dichromate equivalent to 25 mg. of chromium per kilogram of body weight, over a period of 33 days, without ill effects definitely attributable to the chromium.

2. The presence of chromium in the drinking water reduced the water consumption of the rats. The average consumption of water containing 200 mg. chromium per liter was 27% less than the consumption of tap water.

RECOMMENDATIONS.

None.

Medical Division Report No. 105. The Oral Toxicity of Hexavalent Chromium.

I. INTRODUCTION.

A. Object.

The object of this investigation was to determine the effect on albino rats of the oral ingestion of water containing hexavalent chromium.

B. Authority.

Authorized by the Chief, Chemical Corps, under Project D 8.3, Food and Water Supplies in Chemical Corps Test Program No. T3, Cml C Research and Development Program for FY 1944-1945.

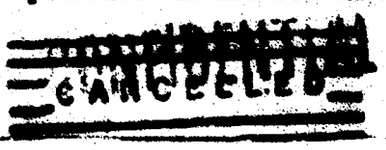
II. HISTORICAL.

The possibility that gas mask canisters might be used for the emergency filtration of water supplies in the field has been suggested as creating a potential health menace to the soldier. This is emphasized by the fact that certain of Whetlerite type gas mask carbons, used in the newer type canisters are capable of imparting hexavalent chromium to water with which they have come in contact. Braidech, (1) by filtering water through standard type army gas mask canisters (MIXA2, MIXA1) found concentrations of hexavalent chromium as high as 54 ppm. Hexavalent chromium concentrations as high as 100 ppm, in water filtered through similar type canisters, have been reported (2).

Recognizing the possibility of canister filtrates containing amounts of hexavalent chromium of this magnitude, the answer to the question of health hazard to individuals lies in the determination of the oral toxicity of hexavalent chromium. Water purified by such an emergency measure would be drunk for no longer than seven days. The concentrations of hexavalent chromium and the period of the test were chosen to give an appreciable safety factor.

The literature furnished very little help on this question of the oral toxicity of hexavalent chromium. Nearly all of the work done on chromium and chromium compounds has been comprised of investigations of the corrosive action of the compounds on the skin, intestinal tract or on the respiratory system when inhaled. These were industrial hygiene rather than oral toxicity investigations. The United States Public Health Service, (3) in its 1942 Water Standards permits no hexavalent chromium in drinking water. A review of the literature disclosed no reports which would support the toxicity thus implied.

Kober and Haythurst (4) quote Lehmann (5) as stating that his feeding experiments on animals, with doses of 2-5 mg. of hexavalent chromium as bichromate per kilogram of body weight continued for 3-16 mo., produced no visible effects. Lehmann (5) further states that in a man of average weight (70 kg.) from 10-30 mg. of potassium dichromate (2-8 mg. chromium) appear to be tolerated without injury and even larger doses have been given for therapeutic effects with good results. Witthaus (6) describes a case where a dose of 2-3 gm. of potassium dichromate taken internally by a man



of 43 years was fatal within ten days. Rabbeno (7) states that the MLD for sodium dichromate when injected intravenously into rabbits is 0.000066 mols per kilogram of body weight, and that potassium dichromate is even more toxic. Kehoe, Cholak and Largent (8) in a comprehensive study of the hygienic significance of certain trace metals in drinking water have classified chromium as a non-nutritive, non-toxic trace element.

Sollman (9) states that the chromates and chromic acid have some toxicologic importance, producing a characteristic nephritis and glycosuria. The fatal dose of potassium dichromate is below 8 gm. According to Kappeler, (10) when bichromates are given by the mouth, they are reduced to chromous oxide and partly deposited as such in numerous organs, the rest being excreted by the organs. An Italian source (11) describes an experiment where 3 mg. daily of hexavalent chromium per kilogram of body weight were injected subcutaneously into rabbits. A qualitative determination for trivalent chromium in the urine was positive throughout the period.

III. EXPERIMENTAL.

A. Procedure.

1. Chromium Solution fed to Rats.

a. Preparation.

Portions of tap water containing 50, 100 and 200 mg. of hexavalent chromium per liter were prepared by dissolving respectively in 6 l. portions of Edgewood tap water 0.85, 1.70, 3.40 gm. of potassium dichromate crystals (Baker's c.p. analysed).

b. Chromium concentration.

The concentration of hexavalent chromium in each of the three solutions to be fed was determined by the method of Graham (12). These concentrations were checked from time to time while the solutions were being used.

2. Selection and Housing of Rats.

Forty-eight healthy young albino rats, 24 male, 24 female, with weights ranging between 50 and 80 gm. were chosen for the experiments. The animals were divided into 4 groups of 12 rats each. Each group included 4 cages, 3 animals per cage. Distribution of rat litters as between groups and cages was such as to insure maximum group uniformity. All rats received a normal diet throughout the experiment.

3. Consumption of Chromium by the Rats.

Water containing 50, 100, 200 mg. hexavalent chromium per liter was fed to groups II, III and IV respectively by means of constant feeding inverted water bottles. This water was available to the rats at all times during the experiment. Bottles were emptied, washed and refilled at least twice weekly. At the beginning of the experiment all groups were fed tap water for six days. Group I continued on tap water throughout the

experiment. Groups II, III and IV were fed chromium containing solution for 33 days. Daily water consumption was determined for each cage of rats. Data on the amount of water consumed by each group and the average water consumption per rat for each group have been summarized in Table I. The latter is also presented graphically in Figure I. Each of the experimental animals was weighed twice weekly. In Table II is shown a summary of the data on the individual rat weights averaged by groups. These data are plotted in Figure II to show the rate of growth curve for each of the four groups.

4. Pathology.*

All of the factors in the experiment were the same, with the exception of the water received.

As animals died in the course of the experiment, they were autopsied and tissues were taken for microscopic study. At the termination of the experimental time of 33 days, the living animals were sacrificed and autopsied. Tissues taken for microscopic study were lungs, spleen, kidneys, adrenals, liver, intestines and bone marrow.

B. Results.

1. Pathology.

a. Group II (50 mg./l.).

One animal died on the sixth day, showing pneumonia accompanied by an abscess.

One animal died on the eleventh day with pneumonia.

Of the ten remaining animals, all of which were sacrificed, two showed moderate amounts of pneumonia, and eight animals showed no pathology.

b. Group III (100 mg./l.).

Of the eleven animals examined in this group, nine were essentially normal, one had a moderate amount of pneumonia, and one had pneumonia with abscess formation.

c. Group IV (200 mg./l.).

Eleven animals were included in this group. One animal died on the nineteenth day with severe pneumonia. Of the ten animals sacrificed, one had a moderate amount of pneumonia and the remaining nine were essentially normal.

* The pathological studies were made by Major Arthur M. Ginaler of the Pathology Section, Medical Division.

d. Group I (Uncontaminated water).

Three of the eleven animals examined in this group showed varying amounts of pneumonia while eight were essentially normal.

2. The amount of water consumed by each group with the average consumption per rat is shown in Table I. Fig. I presents this graphically. The individual rat weights averaged by groups are shown in Table II. Fig. II shows the rate of growth curve for each group of rats during the course of the experiment.

IV. DISCUSSION.

It was noted that Groups II, III and IV reacted immediately to the first feeding of chromium contaminated water:

1. Water consumption in all three groups fell off. The per cent decrease was progressively greater with increasing concentrations of chromium, due to the reduced palatability of the higher concentrations.

2. The rate of growth for the two-day period immediately following the first feeding of chromium was definitely less than the rate for the six-day period preceding.

After several days on the chromium contaminated water, all three groups apparently learned to tolerate the water. Their water consumption then continued at a rate somewhat lower than that of the control rats. The mean daily water intake per rat, averaged by groups, over the thirty-three day period was:

Group I : 18.5 gm. containing no chromium.
Group II : 15.7 gm. containing 50 mg. hexavalent chromium per liter
Group III: 14.5 gm. containing 100 mg. hexavalent chromium per liter
Group IV : 13.4 gm. containing 200 mg. hexavalent chromium per liter

These daily water consumption values represented a daily chromium intake equal to:

Group I : no chromium
Group II : 7.2 mg. hexavalent chromium per kilogram body weight
Group III: 13.1 mg. hexavalent chromium per kilogram body weight
Group IV : 25.0 mg. hexavalent chromium per kilogram body weight

The rates of growth of Groups II, III and IV, after being checked for 2-3 days immediately following the first feeding of the chromium, continued, with deviations probably due to pneumonia, to parallel the growth curve of the control group. The per cent gain in weight for the test period of 33 days, averaged by groups was:

Group I	84%
Group II	71%
Group III	65%
Group IV	66%

The fact that numerous rats, including some in each group, contracted and suffered from pneumonia in varying degrees of severity must be noted. The effect of these cases on both the water consumption and the rate of growth of all groups is obvious. No attempt has been made either to evaluate or to compensate for this factor. The rate of growth in rats drinking the chromium solutions did not differ significantly when compared statistically with the rate of growth of the control animals.

The only pathology found in these animals was the occasional presence of pneumonia. This finding appeared in both the experimental and control animals. Therefore, it can not be said that potassium dichromate was the causative factor in the production of the pneumonia.

From this study it appears that rats are not harmed by the administration of potassium dichromate under the conditions of this experiment.

V. CONCLUSIONS.

1. The test animals drank concentrations of hexavalent chromium as high as 200 mg./l., as potassium dichromate equivalent to 25 mg. of chromium per kilogram of body weight, over a period of 33 days, without ill effects definitely attributable to the chromium.

2. The presence of chromium in the drinking water reduced the water consumption of the rats. The average consumption of water containing 200 mg. chromium per liter was 27% less than the consumption of tap water.

VI. RECOMMENDATIONS.

None.

VII. BIBLIOGRAPHY.

1. M. M. Braidech and H. Gilbert, "Experimental Investigations on Detection of Chemical Warfare Agents in Water and Methods for Their Removal", CWS Contract number: W-49-057-cws-14, July 1, 1945.

2. Medical Division Informal Monthly Progress Report for February 1945.

3. Public Health Reports: Vol. 58, No. 3, January 15, 1943.

4. G. M. Kober and E. R. Hayhurst, "Industrial Health", P. Blakiston's Sons and Co., 1924.

5. K. B. Lehmann, Arbeits U. Gewerbehygiene, Leipsig, 1919.

6. R. A. Witthaus, "Manual of Pharmacology", W. Ward and Co., 1911.

7. A. Babbano, "Review of Chromium Poisoning", Arch. Ital. Sci. 1: (6), 397, 1932.

8. R. A. Kehoe, J. Cholak and R. J. Largent, "The Hygienic Significance of Contamination of Waters with Certain Mineral Constituents", Journal AWWA, 36: 645, June 1944.

9. T. H. Sollman, "A Manual of Pharmacology", 5th Ed., W. B. Saunders Co., Philadelphia, Pa., 1936.

10. Kappeler, Chromate, Inaug. Bonn, 1896.

11. F. Capelli, Med d. lavoro, 30: 111, 206-1939.

12. D. W. Graham, "Chromium - A Water and Sewage Problem". Jour. Amer. Water Works Assoc. 35 (2): 159-165, 1943.

APPENDIX

TABLE I.

SUMMARY OF DAILY WATER CONSUMPTION.

Time	Control		Hexavalent Chromium					
			50 mg./l.		100 mg./l.		200 mg./l.	
Days	GROUP I		GROUP II		GROUP III		GROUP IV	
	Total gm.	Av. gm.	Total gm.	Av. gm.	Total gm.	Av. gm.	Total gm.	Av. gm.
1	163	13.5	147	12.2	154	12.9	159	13.2
2	161	13.4	166	13.9	171	14.3	164	13.7
3	175	14.6	181	15.1	174	14.5	175	14.6
4	183	15.3	180	15.0	188	15.6	177	14.8
5	175	14.6	189	15.7	191	15.9	183	15.2
6	172	14.4	162	13.5	143	11.9	104	8.6
7	197	16.4	169	14.0	155	12.9	115	9.6
8	193	16.1	163	13.6	166	13.8	127	10.6
9	212	17.6	158	13.2	171	14.2	140	11.7
10	219	18.2	185	15.4	193	16.0	162	13.5
11	215	17.9	161	13.4	162	13.5	155	12.9
12	205	17.1	163 (1)	14.8	175	14.6	150	12.5
13	224	18.6	172	15.6	171	14.2	160	13.4
14	211	17.6	165	15.0	179	14.9	168	14.0
15	226	18.8	160	14.5	175	14.5	157	13.1
16	212	17.7	159	14.4	171	14.2	156	13.0
17	226	18.8	174 (2)	17.4	176	14.6	170	14.2
18	228	19.0	169	16.9	191	15.9	172	14.3
19	216	18.0	166	16.6	179	14.9	167	13.9
20	216	18.0	152	15.2	179	15.0	161	13.4
21	222	18.5	161	16.1	189	15.7	167	13.9
22	212	17.7	151	15.1	165	13.8	150	12.5
24	451	18.8	320	16.0	364	15.2	305	12.7
26	482	20.1	340	17.0	363	15.1	302 (3)	15.0
28	456	19.0	341	17.5	349	14.5	314 (4)	15.7
29	210	17.5	158	15.8	165	13.7	144	14.4
31	496	20.7	320	16.0	333	13.9	282	14.1
33	513	21.4	352	17.6	324	13.5	310	15.5
35	494	20.6	356	17.8	374	15.6	288	14.4
36	261	21.7	188	18.8	201	16.8	153	15.3
38	490	20.4	352	17.6	355	14.8	326	16.3

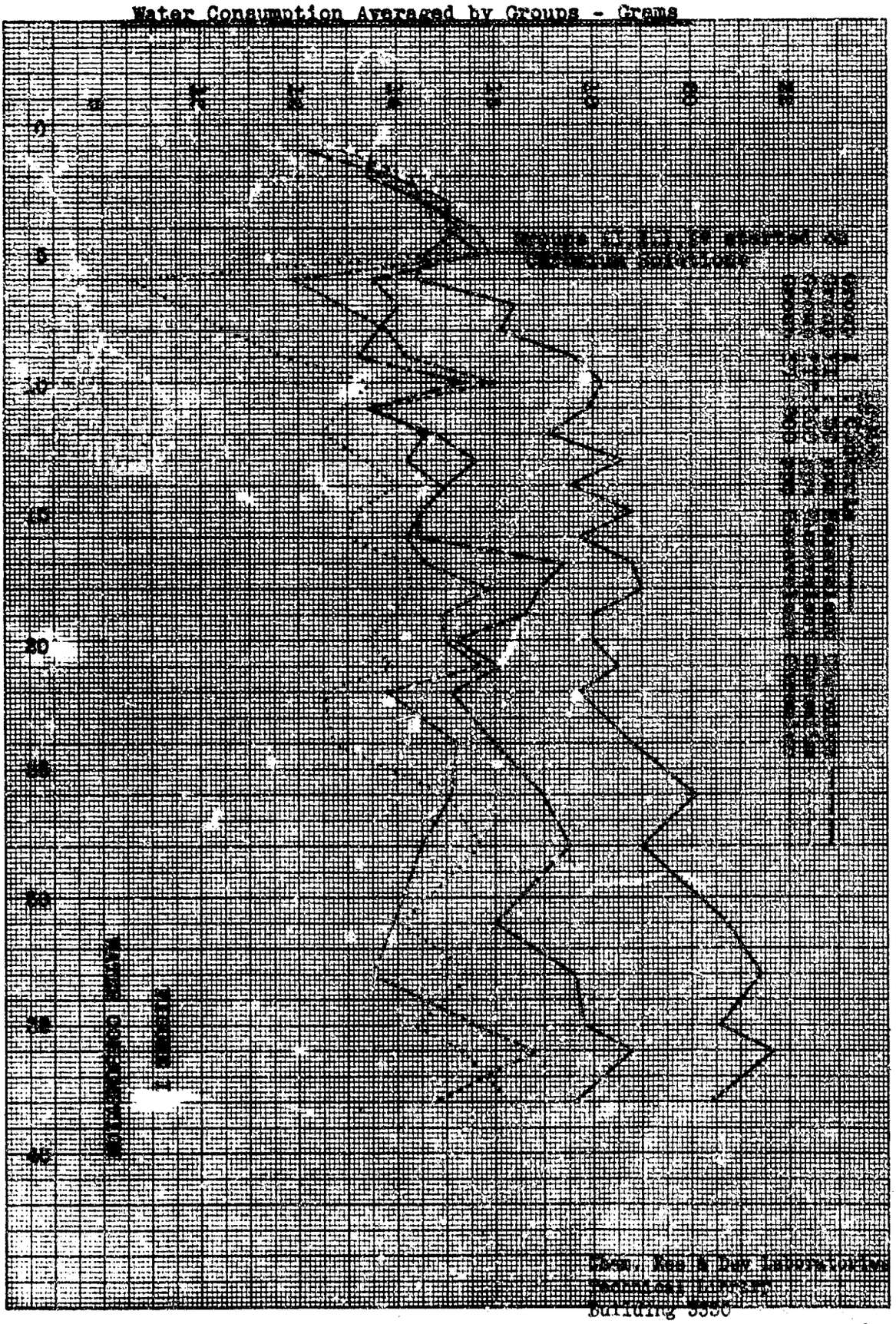
(1) One rat ill - placed in separate cage
(2) One rat ill - placed in separate cage
(3) One rat dead on 24th day
(4) One rat died on 27th day

TABLE II

SUMMARY OF RATE OF GROWTH IN RATS

Time	Control		Hexavalent Chromium					
			50 mg./l.		100 mg./l.		200 mg./l.	
Days	GROUP I		GROUP II		GROUP III		GROUP IV	
	Total gm.	Av. gm.	Total gm.	Av. gm.	Total gm.	Av. gm.	Total gm.	Av. gm.
0	782	65	688	69	795	66	687	69
3	891	74	770	77	894	75	781	78
5	960	80	836	84	990	83	846	85
7	1010	84	871	87	1023	85	839	84
10	1103	92	930	93	1110	93	900	90
12	1150	96	962	96	1165	97	945	95
14	1188	99	989	99	1216	101	982	98
17	1255	105	1039	104	1274	106	1032	103
19	129[illegible]	108	1083	108	1326	111	1082	108
22	1355	113	1123	112	1391	116	1142	114
24	409	117	1151	115	1422	119	1151	115
26	1464	122	1187	119	1458	122	1189	120
28	1502	125	1215	122	1484	124	1234	123
31	1584	132	1270	127	1498	125	1271	127
33	1624	135	1315	132	1515	126	1314	131
35	1692	141	1355	136	1571	131	1326	133
38	1768	147	1436	144	1638	137	1406	141

Water Consumption Averaged by Groups - Grams



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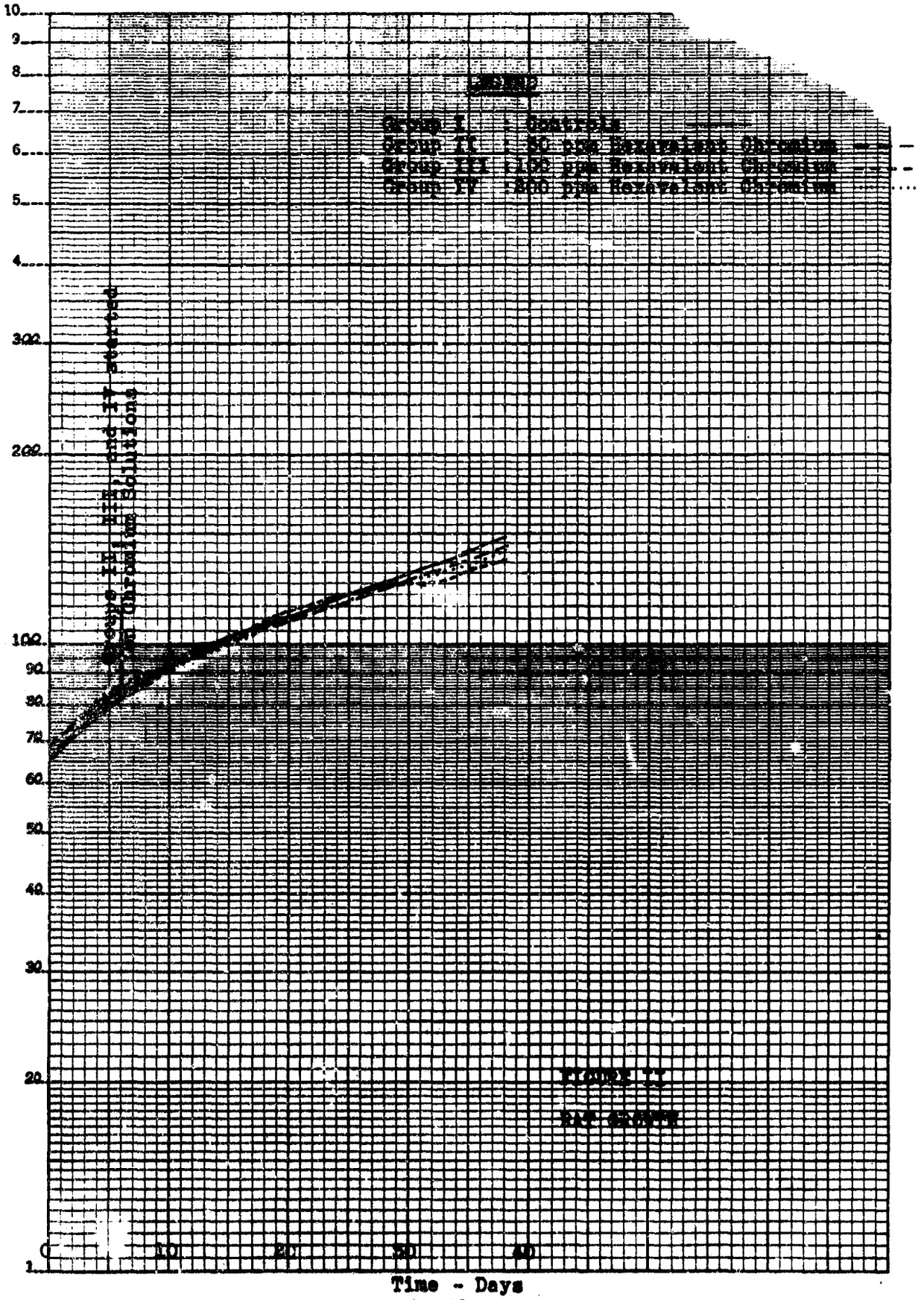

FIGURE IV

RAT GROWTH

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...e Oral Toxicity of Hexavalent Chromium.

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